

89. (Amended) The A method of claim 23, wherein the peptidyl PYY agonist is for treating a disease associated with altered glucose metabolism, comprising administering to an animal identified as having a disease associated with altered glucose metabolism an amount of a composition comprising PYY, wherein the amount of PYY is sufficient to increase the glucose responsiveness of a pancreatic islet or cell in the animal.

90. (Amended) The A method of claim 33, wherein the peptidyl PYY agonist is for maintaining or restoring a function of pancreatic  $\beta$  cells, comprising administering to a pancreatic islet or cell a composition comprising PYY, thereby maintaining or restoring a function of pancreatic  $\beta$  cells.

91. (Amended) The A method of claim 45, wherein the peptidyl PYY agonist is for maintaining or restoring normal pancreatic islet function, comprising administering to a cultured pancreatic islet or cell PYY, thereby maintaining or restoring normal pancreatic islet function.

### REMARKS

Claims 1-13 and 15-91 constitute the pending claims in the present application. Claims 1-12, 24-27, 34-38, 40, 41, 44, 47-49, and 52 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter. Applicants submit, however, that claims 25-27, 34-37, 52, and 53-86 are properly dependent on elected independent claims and should be considered together upon determining that such independent claims are allowable, pursuant to MPEP 809.02(c). Accordingly, all of these claims are presented above. Applicants cancel, without prejudice, claims 51 and 63. Applicants add new claims 92-95. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114, and Applicants' previous submission has been entered.

2. Claims 30, 31 and 39 are objected to for being dependent upon a canceled claim. Applicants' amendments are believed to obviate the objection.
3. Claims 13, 15-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78, 85 and 87-91 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The basis of this rejection appears to be three-fold. Firstly, the Examiner alleges that the application is not enabled for methods comprising administration of PYY agonists and DPIV inhibitors, insulin or GLP-1. Secondly, the Examiner alleges that the application is not enabled for methods of promoting maturation. Thirdly, the Examiner alleges that the application is not enabled for PYY agonists other than PYY.

Applicants respectfully traverse the first ground of rejection. The specification provides ample support for methods employing conjoint therapy, wherein both a PYY agonist and a DPIV inhibitor, insulin or GLP-1 are administered (see, for example, page 36, lines 13-23). The Examiner appears to be alleging that, in the absence of specific data demonstrating the co-administration of these agents, Applicants are not entitled to claims directed to this subject matter. This position is inconsistent with the MPEP. In accordance with MPEP 2164.02, “[a]n example may be either working or prophetic. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.”

Applicants have provided working examples demonstrating that PYY can be used effectively to stimulate insulin release in glucose challenged mice. Applicants have further provided prophetic examples employing conjoint therapies. These prophetic examples can be easily evaluated based on the methods disclosed by Applicants. For example, conjoint therapies can be evaluated using the mouse models provided in the specification which were used to evaluate the efficacy of PYY administration. Given the ample teachings provided in the application, the efficacy of conjoint therapies can be readily evaluated without undue experimentation.

MPEP 2164.04 outlines the criteria for evaluating enablement. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

The reasoning outlined in MPEP 2164.04 is well support by the Court which stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Applicants point out that the specification provides ample support for conjoint therapy, and the Examiner has provided no evidence or factual basis to doubt the veracity of Applicants' disclosure. Furthermore, Applicants point out that the subject methods for employing conjoint therapy, as outlined in detail in the specification, build upon current methods that are used in the treatment of individuals with disorders characterized by defects in glucose-metabolism. For example, administration of insulin is part of the standard of care for diabetics. Absent specific evidence to the contrary, Applicants contend that one of skill in the art would have no reason to doubt that currently employed therapies, such as administration of insulin, can be combined with methods disclosed in the present application to provide conjoint therapies.

In light of the knowledge available to one of skill in the art and the teachings of the specification, Applicants contend that there is no reason to doubt Applicants' prophetic examples using conjoint therapy. In the event that the Examiner opts to maintain this ground of rejection, Applicants respectfully request that the Examiner make of record specific evidence used to

support the rejection so that Applicants will have the opportunity to specifically address concerns raised by this evidence.

In response to the second ground of rejection, the Examiner has alleged that the specification fails to enable methods of promoting pancreatic islet maturation. Applicants admit that they do not understand the basis for this rejection. The Examiner has agreed that Applicants have demonstrated the use of the subject methods for promoting glucose responsiveness, but alleges that this is insufficient to demonstrate the use of the subject methods for promoting maturation. Applicants maintain the arguments of record and contend that glucose responsiveness is an excellent indicator of maturation. The Examiner has cited characteristics such as marker expression and morphology as more indicative of maturation. However, in contrast to the characteristics suggested by the Examiner, the characteristic of glucose-responsiveness provided by Applicants is reflective of the functionality of the cells. This functional characteristic is a reasonable indicator of islet maturation, and defines the state of the cells' maturation no less particularly or reliably than markers or other physical features.

Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have canceled claim 51. Cancellation of claim 51 is not in acquiescence of the rejection and Applicants reserve the right to prosecute claims of similar or differing scope.

The final ground for rejection under 35 U.S.C. 112, first paragraph, is based on the enablement of peptidyl PYY agonists. The Examiner has alleged that this term is overly broad and encompasses variants of PYY which may or may not retain the function of the PYY polypeptide, as presented in SEQ ID NO: 3. To expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more explicitly point out the claimed subject matter. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

The amended claims are explicitly directed to the use of PYY agonists comprising polypeptides which have a specific structural relationship to the PYY polypeptide provided in the application. Literal support for Applicants' amendments can be found on page 6, lines 1-9 and page 21, lines 30-33. Furthermore, Applicants point out such PYY agonists are described not only with reference to sequence and structural information, but also with reference to their

function. Accordingly, one of skill in the art can readily recognize and appreciate the PYY agonists for use in the claimed methods.

The Examiner has cited Wells to support the notion that because changes in primary sequence can affect the function of a protein or peptide, Applicants are not entitled to claims directed to the use of a broader range of PYY agonists. In response to this argument, Applicants raise the following two points. Firstly, even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), “[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.” This standard has been upheld in the courts, and permits a claim to encompass a finite number of inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). Applicants additionally note however, that given the functional limitations expressly recited in the claims, PYY variant sequences which do not retain the recited function do not fall within the scope of the claims.

Secondly, Applicants point out that the Wells reference relied upon by the Examiner was published in 1990. Since that time, there has been a veritable explosion in the art of combinatorial chemistry which readily allows the making and testing of polypeptide variants without undue experimentation. Thus, even if one agrees that small differences in polypeptide sequence can affect the function of a protein or peptide, this point is immaterial in assessing the enablement of the claimed methods. Rather, the important consideration in determining whether Applicants have enabled the use of PYY variants in the subject methods is whether one of skill in the art could readily make and test polypeptide variants using the teachings of the specification and the state of the art, without undue experimentation, in order to select PYY variants for use in the subject methods. Applicants contend that this burden has been met.

The specification provides a detailed description of methods of making and testing variants using combinatorial mutagenesis (page 22, line 24-page 23, line 17). Furthermore, as

noted above, the specification provides mouse models in which PYY variants can be tested for efficacy in the subject methods. Given the extensive guidance provided in the specification, as well as the high level of skill in the art, Applicants contend that one of skill in the art can readily make and test PYY variants to identify variants which meet the structural and functional limitations recited in the claims without undue experimentation.

Additionally however, Applicants are not merely relying upon the ability of one of skill in the art to make and test peptide variants in order to select variants for use in the methods of the present invention. Applicants reiterate the arguments of record, and remind the Examiner that several PYY variants have been identified and the ability of these variants to mimic one or more functions of PYY has been demonstrated. Accordingly, these examples demonstrate that not only **could** one of skill in the art make and test variants to identify those variants with particular functional attributes, but one of skill in the art **did** make and test variants to identify variants with particular attributes. In light of Applicants' amendments and arguments, Applicants contend that the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection is respectfully requested.

4. Claims 13, 15-23, 28-33, 39, 45, 46, 50, 51, 53, 54, 57-60, 63, 76-78 and 85 are rejected under 35 U.S.C. 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The Office Action alleges that the metes and bounds of the term "peptidyl PYY agonist" cannot be readily determined. Applicants disagree with this statement. The specification provides ample discussion and an extensive number of examples such that one of skill in the art can readily appreciate the term "PYY agonist" (see, for example, page 14, lines 4-19). Furthermore, the term "peptidyl" is art-recognized, and one of skill can readily appreciate its plain meaning. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out certain embodiments enumerated in the specification. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

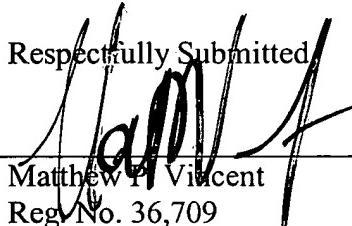
5. Applicants additionally note that the specification has been amended to correct an obvious error in referring to an amino acid sequence. The specification previously identified the amino acid sequence presented on page 21 as SEQ ID NO: 1, however the sequence listing filed with the application refers to a nucleic acid sequence as SEQ ID NO: 1. One of skill in the art would readily appreciate that the reference to the amino acid sequence presented on page 21 as SEQ ID NO:1 was a clerical error and this sequence must instead be referred to using a different sequence identifier. Additionally, Applicants enclosed herewith an amended sequence listing which appropriately refers to SEQ ID NO: 3.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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